Chapter

General introduction
and thesis outline
Introduction

Mrs. Bakker is a 69-year old woman, who used to teach English at a high school in her neighborhood. Three years ago, she retired and together with her husband she started singing in a choir and joined a weekly cycling group. Mrs. Bakker was brilliant in remembering the names of all the children in her classes. However, lately she is experiencing trouble remembering the names of new choir members. Mrs. Bakker noticed that her husband does not know all their names either. But he did not put any effort in remembering names like her. Mrs. Bakker functions independently and no one has ever told her that she had forgotten something important. She worries that her memory is getting worse and that she might have dementia. After a consultation at her general practitioner, Mrs. Bakker visits a memory clinic for a clinical work-up. After two weeks, the neurologist explains to her that all memory scores were normal. Mrs. Bakker is happy to hear that she does not have dementia. However, Mrs. Bakker would like to know what she can do to keep her brain as healthy as possible [fictive case].

Dementia, a global health problem

Dementia is characterized by an impairment in cognitive functioning (Box 1) that leads to problems in daily life [1]. The number of people living with dementia worldwide is increasing due to the aging of the population [2]. In 2018, 50 million people were living with dementia and it is estimated that this number will triple in the next 30 years [3]. Dementia is a great burden for the health care system. In the Netherlands, dementia accounts for approximately 8% of all health care costs [4]. There is a need for effective, potentially non-pharmaceutical, interventions to fight this global health problem.

(Box 1) Cognitive functioning is an umbrella term for mental processes and actions that allow us to think, process and remember information and perceive the environment. These functions allow us to perform complex tasks, such as cooking a meal or driving a car. Cognitive functioning can be divided into cognitive domains including verbal memory, organization, attention, spatial reasoning and language, and can be assessed using neuropsychological tests. The results indicate whether cognitive functioning is normal or impaired, and in case of an impairment give insight in which cognitive domains are affected. One of the defining characteristics of dementia is the impairment of two or more cognitive domains [1]. In addition, cognitive functioning is declined from a previous level and interferes with independence in activities of daily living. The cognitive impairment should not be attributable to psychiatric disorders or a delirium. Dementia develops gradually and often is preceded by a phase of cognitive impairment that does not fulfill the criteria for a dementia diagnosis, so called mild cognitive impairment (MCI) [6].
The most common cause of dementia is Alzheimer’s disease, a neurodegenerative disease accounting for 60 to 80% of all dementia cases [5]. Other causes include vascular dementia, frontotemporal dementia and dementia with Lewy bodies. Currently, there is no treatment available to cure or to delay the course of the diseases causing dementia. Diseases that cause dementia have a so-called pre-dementia phase, for example a mild cognitive impairment but no interference in daily life. This phase offers a window for interventions to treat, delay or prevent dementia.

**Lifestyle-based dementia prevention**

In the absence of a treatment for dementia, it is important to decrease the risk of developing dementia or to delay the onset of dementia. Therefore, risk factors and protective factors that are related to the development of dementia are of interest. Research has increasingly focused on lifestyle (Box 2). It is estimated that up to 30% of all dementia cases are attributable to modifiable risk factors, including lifestyle factors. Examples are physical activity, social activity, mood and smoking [7-9]. This theoretical model implies that we would be able to prevent new dementia cases by eliminating these risk factors.

Nutrition is one of the lifestyle factors that has been studied extensively in relation to health and in which also patients are very interested. Evidence on the benefits of healthy nutrition for brain health is growing [10, 11]. Some studies investigated the relation between specific nutrients (e.g. vitamins) or single foods (e.g. fatty fish or red wine) and cognitive decline. However, foods are usually not consumed in isolation, but are combined in meals that together form a complete diet. Foods can also have an additive effect, which would not be captured when studying single foods. Therefore, an increasing number of studies is now focusing on complete dietary patterns [12]. The Mediterranean diet [13] and the MIND-diet [14, 15] are examples of diets that are increasingly studied and seem to be beneficial for cognitive decline and risk of dementia [16]. Nutrition was found to improve blood pressure, glucose levels, oxidative stress and inflammation processes [17-21], which are also important for maintaining brain health. However, more research is needed to disentangle the biological mechanisms behind these effects.

Studying lifestyle and cognition is challenging due to the many methodological considerations. Both lifestyle and cognition are complex constructs and in addition are influenced by many personal and environmental factors. Therefore, it is difficult to disentangle the effect of single, let alone a combination, of multiple lifestyle factors on brain health. While the effect of single interventions are of interest to investigate the mechanisms by which they exert a beneficial effect on brain health, multi domain lifestyle interventions have been suggested to be more effective than interventions that cover a single domain [22-24]. Promising findings of lifestyle-based interventions are accumulating [25], increasing the interest to explore lifestyle as a target for brain health promote.
An attractive option is to offer such lifestyle-based brain health promotion online, making use of the rapidly developing landscape of eHealth [26]. Online programs have several advantages over face-to-face programs. An online program has the opportunity to reach larger audiences, since the majority of people have access to the internet [27]. In addition, online programs could be cost-effective in long-term, since costs per person are relatively low. Also, access to an online program is flexible regarding time and location, making online programs fit more easily in personal schedules and thereby potentially increasing adherence to the program. While online programs have the potential to contribute to lifestyle changes [28, 29], online interventions often have difficulties maintaining good adherence rates [30, 31]. This means that people that start to use the program, often stop before the end of the program. EHealth experts recommended to involve all stakeholders in the development of an online program. In this process of co-creation the users give input during all phases of development. A program would then better fit the users preferences, which has been shown to benefit user satisfaction and adherence [32-34]. These factors are of importance when aiming to develop a useful and sustainable online program. At the moment, there is no information available on which online lifestyle programs for brain health have been developed and how information should be offered online in order to fit the needs of non-demented older individuals.

Targeting at-risk individuals
It is crucial to select the appropriate target population for a specific intervention. Most studies on the relationship between lifestyle and cognitive functioning have been conducted in healthy elderly from the general population. These results cannot simply be generalized to clinical populations. In individuals with cognitive impairment, for example, brain changes might have occurred [35]. In addition, individuals might change their lifestyle when they notice cognitive changes or after receiving a diagnosis. This means that the link between lifestyle and brain health could differ between healthy elderly and those with cognitive impairment.

Studies have suggested that lifestyle interventions may be especially effective in individuals at-risk for cognitive decline. For illustration, in a study that evaluated the effect of a multi domain lifestyle intervention with or without supplemental omega 3 polyunsaturated fatty acids [36], the total group did not show a benefit of the intervention. However, the researchers also specifically looked into the effect
of the intervention in individuals with an increased risk for cognitive decline. This subgroup had a higher cardiovascular risk factor (CAIDE) score, or abnormal amyloid (Alzheimer’s disease related proteins) levels in the brain. Results showed that the multi domain lifestyle intervention was effective in these individuals at increased risk of cognitive decline.

While individuals in the before mentioned study were at-risk for cognitive decline based on physical characteristics, individuals can also be at-risk based on subjective cognitive complaints (Box 3). Since we know that brain changes precede cognitive impairment by decades [35], individuals at risk for cognitive decline but without objective cognitive impairment might already have small brain changes and might be in a very early phase of a disease that causes dementia. In addition, individuals reporting cognitive complaints in the memory clinic are interested in brain health and generally motivated to participate in studies. For these reasons, individuals that are at risk because of SCD are a very interesting target group for brain health initiatives.

(BOX 3) Individuals with cognitive complaints may visit a memory clinic with worries about a neurodegenerative disease. When results of extensive neurological and neuropsychological assessments are normal, people are labeled as having ‘subjective cognitive decline’ (SCD), since the cognitive decline that they experience could not be objectified. At a group level, these individuals are at increased risk for developing dementia [37]. This means that compared to a group of older adults of the same age and level of education but without cognitive complaints, a significant higher percentage of this group eventually will develop dementia. Individuals with SCD that do develop a cognitive impairment and ultimately dementia, have various underlying diseases, such as Alzheimer’s disease, but also vascular dementia [38]. A group of individuals with SCD is therefore enriched with at-risk individuals and therefore very interesting for research that focusses on early stages of neurodegenerative diseases. Most individuals with SCD will, however, not develop a dementia. Still, these individuals report worries and are looking for ways to contribute to their own brain health.

Knowledge of dementia, risk factors and prevention
The need for global brain health initiatives was underlined by the World Health Organization (WHO) in the Global Action Plan on dementia [39], that emphasized the need for campaigns to increase public awareness and understanding of dementia, dementia risk factors and prevention. This issue has been highlighted by studies showing that knowledge about prevention and treatment of dementia remains poor. For example, a recent study found that almost half of the participants believed that dementia is a normal part of ageing and that it is not preventable [40]. Another study found that most respondents believed it is possible to improve brain health and decrease dementia risk. However, one third reported not feeling confident to take action to reduce their personal dementia risk themselves [41]. These studies
emphasize the need for adequate education on dementia prevention and brain health promotion.

Rationale and aims of this thesis

Dementia is an increasing global problem and there is a need for brain health promotion and lifestyle-based dementia prevention initiatives. Lifestyle, including nutrition, contributes to brain health. Since most studies on the relation of nutrition and brain health have been conducted in population-based samples, knowledge on this matter in clinically relevant samples is needed. Further, offering a lifestyle-based brain health program online would increase the outreach of the program. Individuals at-risk for cognitive decline, particularly based on SCD, could be an ideal target group. Insight in the preferences of individuals with SCD and co-creation during the development of an online lifestyle program is necessary for acceptance and successful implementation of the program in later phases.

The studies in this thesis investigate lifestyle in relation to brain health and cognitive functioning in non-demented elderly, in the context of dementia prevention. The aims of this thesis were:

1) to investigate the association of nutrition and cognitive functioning, and
2) to develop and user-test an online lifestyle program for brain health in co-creation with individuals with SCD.

Part I: The first part of this thesis addresses the first aim. In chapter 2 we investigated the association of dietary quality and clinical characteristics, including global cognition, cognitive complaints and depressive symptoms, in a memory clinic-based sample of individuals with SCD. In chapter 3 we then investigated whether nutritional intake was associated with cognition, as measured with an extensive neuropsychological battery, in a German sample of non-demented individuals consisting of healthy controls, individuals with SCD or MCI and first relatives of AD patients.

Part II: The second part of this thesis is dedicated to the development of an online lifestyle program for brain health. In chapter 4 we performed a systematic review and meta-analysis of online lifestyle programs to optimize brain health. Based on this overview, we identified room for improvement and made recommendations for online lifestyle programs in the context of dementia prevention. Then, in chapter 5, we investigated the wishes and preferences of individuals with SCD for an online lifestyle program on brain health. These findings were used as a basis for the development of the online lifestyle program. In an iterative process together with the users and a technical party, we evaluated and adapted the program. In chapter 6, we investigated the user-experiences of individuals with SCD of the online lifestyle program. Finally, in chapter 7, we summarize the main findings and discuss the results of this thesis. We conclude this thesis with suggestions for further research.
REFERENCES


